A sinister black finding in the stomach

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A 68-year old woman undergoing a routine surveillance endoscopy—part of her follow-up for a Barrett's oesophagus—was found to have a solitary, 4 mm, black lesion in the gastric body (Figure A). Biopsies were taken which showed mucosa typical of the gastric body with heavily pigmented cells within the lamina propria infiltrating around the crypts without destroying them (Figure B). Immunohistochemical examination of biopsied tissue section showed positive staining for melanoma associated antigens using antibodies including Melan-A, HMB-45, MITF, and SOX-10. Her medical history included the enucleation of her left eye 13 years earlier to remove a primary uveal melanoma; she had been discharged from routine follow-up. We then decided to carry out another gastroscopy to take deeper gastric biopsies. These showed infiltration of the muscularis mucosae by melanocytes with mild atypia. A full-body CT scan showed multiple lesions in her liver which on subsequent MRI were confirmed to be melanin-laden metastases (Figure C). Gene mutation panel testing on the gastric biopsy specimens and on the ocular specimens taken at the time of the eye operation 13 years earlier, showed the same oncogenic mutation: Gln209Leu in *GNA11*. Tests for the common cutaneous melanoma mutations in *BRAF*, *NRAS*, and *KIT* genes were negative. The patient was enrolled in a clinical trial testing a combination of selumetinib and paclitaxel chemotherapy for metastatic uveal melanoma.

Uveal melanoma is a rare cancer representing less than 5% of all melanomas; it has a nearly 50-fold lower incidence rate compared with that of cutaneous melanomas. It is an aggressive disease predominantly spreading to the liver in up to 50% of patients. Median survival with liver metastases is under 6 months. Currently, there are no effective non-surgical treatments for metastatic uveal melanoma. Surveillance and monitoring of the liver—after treatment of the primary lesion—is recommended so that patients can receive early locoregional treatments. The length of time patients should be followed-up is not established in current clinical guidelines. Uveal melanoma is associated with an almost linear continuation of recurrence over time and beyond 10 years without a plateau in risk of recurrence over time. Thus, late recurrences are not uncommon: 5- and 10-year cumulative metastasis rate is 25% and 34%, respectively. Cutaneous and uveal melanomas are biologically distinct. Uveal melanomas lack the typical

cutaneous melanoma-associated mutations in the *BRAF*, *NRAS* and *NF1* genes, but have somatic mutations in the *GNA11* and *QNAQ* genes in around 90% of cases—in cutaneous melanomas mutations in these genes are found in less than 10% of cases. Mutations in these genes activate the MAP kinase oncogenic pathway, providing a rationale for using MEK1/2 inhibitors, selumetinib for example, as agents in clinical trials results—although to date the results have been disappointing. Functionally activating mutations in *GNAQ* and *GNA11*, as well as in *CYSLTR2* and *PLCB4*, leads to the subsequent activation of pathways—which include the PI3kinase and Yap/Hippo pathways—downstream beyond the MAP kinase pathway. These may offer potential novel therapeutic targets. Genetic profiling of primary uveal melanomas has some prognostic value. For example, inactivating mutations in the *BAP1* gene—found in approximately 50% of cases—are highly likely to metastasise, whereas mutations in the *SF3B1* and *EIF1AX* genes, occurring in approximately 19% and 24% of uveal melanoma cases respectively, are less likely to metastasise.

Contributors

WJ and PC searched the literature and analysed the results. RCF and MdP cared for the patient. WJ, PC, RCF and MdP wrote the report. WJ and MdP did the endoscopy and provided the images. HL did the genetic analysis. JC did the histological assessment and provided the images. All authors critically revised the report. Written consent for publication was obtained from the patient.

Figure: Surprise black finding at routine endoscopy for Barrett's oesophagus
(A) Solitary, 4mm, black lesion on the greater curvature of the mid-gastric body seen at endoscopy. (B) Typical gastric body mucosa shows heavily pigmented cells within the lamina propria infiltrating around the crypts (haematoxylin and eosin stain). Original magnification x 5. (C) Contrast-enhanced MRI shows multiple T1-hyperintense lesions in the liver—the largest measured up to 2 cm. The lesions were hypointense on T2-weighted and diffusion-weighted imaging.